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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/912,252	CROZE ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/21/05 has been entered.

New claims 28-41 are pending in the present application.

Claims 28-41 are examined on the merits herein, with the previously elected embodiment of increasing the number of functional IFNAR2c receptor chains on the surface of cells within a target cell population by introducing an exogenous gene encoding the IFNAR2c polypeptide in the amendment filed on 7/17/03.

Response to Amendment

The rejection under 35 U.S.C. 102(b) as being anticipated by Domanski et al. (J. Biol. Chem. 273:3144-3147, 1998) is withdrawn in light of Applicants' amendment.

The rejection under 35 U.S.C. 102(b) as being anticipated by Lutfalla et al. (EMBO J. 14:5100-5108, 1995) is withdrawn in light of Applicants' amendment.

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-37 and 40-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***This is a new ground of rejection necessitated by Applicants' amendment.***

Claim 28 and its dependent claims recite "a method of inhibiting cell proliferation in a human target cell population". There is literally **no written support** for the concept of **simply inhibiting cell proliferation in a human target cell population** by increasing the number of functional human IFNAR2c polypeptide chains on the surface of cells within said target cell population by introducing an exogenous gene encoding a human IFNAR2c polypeptide (elected invention) in the originally filed specification. The originally filed specification teaches specifically methods of **potentiating the effects** of effector ligands or **enhancing the effects** of the effector ligands, including anti-growth effects by a type I interferon, by increasing the number of functional receptors for receptor ligands on the cell surface (see at least pages 1-2, original set of claims and the title of the present invention which is "Use of the interferon receptor 2c polypeptide chain to enhance the anti-growth effects of type I interferons"). **Thus, it is apparent that Applicants do not specifically contemplate** a method of inhibiting cell proliferation in a human target cell population, but rather a method of potentiating or enhancing anti-growth effects of a type I interferon in a human target cell population

beyond the anti-growth effects that would result from the administration of a therapeutically effective amount of a human type I interferon alone.

Therefore, given the lack of guidance provided by the originally filed specification, it would appear that Applicants did not contemplate or have possession of the claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-41 are rejected under 35 U.S.C. 112, first paragraph, because with respect to the elected invention the specification, while being enabling for:

A method of potentiating anti-growth activity of a type I interferon (IFN) on human tumor cells, wherein said tumor cells possess functional interferon alpha receptor 2c (IFNAR2c) polypeptide chains, said method comprises the steps of: introducing directly into said tumor cells an exogenous gene encoding a human interferon receptor 2c receptor polypeptide and contacting the modified tumor cells with a therapeutically effective amount of a human type I IFN, and wherein the modified tumor cells possess an increased number of functional IFNAR2c receptor polypeptide chains;

does not reasonably provide enablement for a method of potentiating anti-growth activity of a type I interferon (IFN) on any human target cell population by introducing into said cells an exogenous gene encoding a human IFNAR2c polypeptide by any

route of delivery. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. ***This is a new ground of rejection.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The specification teaches by exemplification showing that various human tumor cell lines (HT1080 cells, U5A cells, MDA231 cells) exhibit **enhanced sensitivity** to the antiproliferative effects (including apoptosis) of IFNβ1b or IFNα upon transfection with a human IFNAR2c gene. Applicants further demonstrated that LOX human melanoma cells transfected with a human IFNAR2c gene are also **more sensitive** to the *in vivo* anti-growth activity of IFNβ1b than the parental LOX cells. The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

(1) The breadth of the claims

With respect to the elected invention, the instant claims encompass a method of potentiating an anti-growth activity of any type I IFN in any human target cell population, wherein said target cell population possesses functional IFNAR2c polypeptide chains,

said method comprising the steps of increasing the number of functional IFNAR2c receptor chains on the surface of cells within the target cell population by introducing an exogenous gene encoding a human IFNAR2c polypeptide into the cells by any route of delivery, and contacting the modified cells with a therapeutically effective amount of a human type I IFN.

(2) The state and unpredictability of the prior art

An embodiment of the elected invention falls within the realm of gene therapy. At the effective filing date of the present application (7/26/00), the attainment of any desired therapeutic effect (for this instance the desired therapeutic effect includes potentiating cell proliferation inhibition activity of a type I IFN in any human target cell population) remains unpredictable. Particularly, vector targeting *in vivo* to targeted cells, tissues or organ continues to be inefficient and unpredictable. This is supported by numerous teachings available in the art. Dang et al. (Clin. Cancer Res. 5:471-474, 1999; Cited previously) noted that further advancement in all fields such as gene delivery, gene expression and host immune manipulation is needed to make gene therapy a reality. Dang et al. pointed out several factors limiting an effective gene therapy, including sub-optimal vectors, the lack of a stable *in vivo* transgene expression, the adverse host immunological responses to the delivered vectors and most importantly an efficient gene delivery to target tissues or cells (last paragraph, col. 2, page 474). Verma & Somia (Nature 389:239-242,1997; Cited previously) reviewed various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that resolution to *in vivo* vector targeting had

not been achieved in the art (see the entire article). Verma & Somia also discussed the role of the immune system in inhibiting an efficient targeting of viral vectors to desired target cells (see page 239, and second and third columns of page 242). More recent reviews by Romano et al. (Stem Cells 18:19-39, 2000; Cited previously) and Xu et al. (Clin. Cancer Res. 7:3314-3324, 2001; Cited previously) also support the lack of an efficient gene delivery to target tissues or cells by any route of delivery to obtain the desired therapeutic effects.

Additionally, at the effective filing date of the present application little was known on the use of an exogenous gene encoding the IFNAR2c polypeptide for potentiating any effect of a type I IFN on any human target cell population, and wherein said target cell population already possesses functional IFNAR2c polypeptide chains as evidenced by the teachings of Johns et al. (U.S. Patent No. 5,681,558; Cited previously), Domanski et al. (J. Biol. Chem. 273:3144-3147, 1998; Cited previously), Platanias et al. (J. Biol. Chem. 273:5577-5581, 1998), and Chen et al. (U.S. Patent No. 6,569,420; Cited previously). Moreover, even several years after the effective filing date of the present application and on the basis of the same set of data presented in the instant specification Applicants still state "It should be noted, however, that our current study utilized only immortalized cultured cells and **it is possible** that enhanced expression of IFNAR2c on **a primary non-cancerous cell may likewise sensitize them to the effects of IFN**. Unlike the cancer cell lines analyzed in our current study, **it is not known if IFNAR2c expression is rate limiting in primary non-cancerous cells**. Therefore, clinically, it may be necessary to specifically deliver the IFNAR2c gene to a

metastasized cancer cell or solid tumor *in vivo*" (page 41, right hand column, first paragraph, Int. J. Cancer 111:32-42, 2004; IDS).

(3) The amount of direction or guidance provided

Apart from the exemplification showing that the increased exogenous expression of functional IFNAR2c receptor polypeptides in various transfected human cancer cell lines; some of which possess functional IFNAR2c polypeptide chains, resulted in enhanced sensitivity of the transfected cells to the antiproliferative effects (including enhanced apoptosis) of IFNβ1b or IFNα, the instant specification fails to provide sufficient guidance for a skilled artisan on how to attain a similar enhanced antipoliferative activity of a type I interferon on any other human target cell populations. Despite the ability of all type I interferons to bind to the same type I interferon receptor, it should be noted that differences in signaling and biological effects exist among them as well as the cell types on which the interferons act on (Domanski et al., J. Biol. Chem. 273:3144-3147, 1998; Platanias et al., J. Biol. Chem. 273:5577-5581, 1998). Several years after the effective filing date of the present application Applicants still state "It should be noted, however, that our current study utilized only immortalized cultured cells and **it is possible** that enhanced expression of IFNAR2c on **a primary non-cancerous cell may likewise sensitize them to the effects of IFN**. Unlike the cancer cell lines analyzed in our current study, **it is not known if IFNAR2c expression is rate limiting in primary non-cancerous cells**" (page 41, right hand column, first paragraph, Int. J. Cancer 111:32-42, 2004; IDS). Therefore, it is not clear that the increase in an exogenous expression of a human IFNAR2c receptor in any human target cell

population would necessarily potentiate an inhibitory cell proliferation activity of a type I IFN. Since the prior art at the effective filing date of the present disclosure does not provide such guidance, it is incumbent upon the instant specification to do so.

Additionally, the present application fails to provide sufficient guidance for a skilled artisan on how to overcome obstacles associated with *in vivo* vector targeting known in the art as discussed above, so that cells of any human target cell population can be transfected efficiently with an exogenous gene encoding the IFNAR2c polypeptide by any route of delivery to yield the desired therapeutic effects. Particularly, with respect to an embodiment of claim 37, neither the present application nor the prior art teaches a skilled artisan on how to use electroporation for introducing an exogenous gene encoding a human IFNAR2c polypeptide efficiently into any human target cell population *in vivo* to yield the therapeutic effect contemplated by Applicants. In light of the state of the art and given the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

(4) Working example provided

The specification fails to provide an example showing an enhanced antiproliferative effect of a type I IFN has been achieved for any non-cancerous human target cell population apart from exemplified tumor cell lines. The instant disclosure also fails to provide any example demonstrating that hurdles in *in vivo* vector targeting known in the art has been overcome and desired therapeutic effects have been attained.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the breadth of the claims, and the unpredictability of the gene therapy art, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Response to Arguments

Applicants' arguments related in part to the above rejection in the Amendment filed on 3/21/05 (pages 4-5) have been fully considered, but they are not found persuasive.

Applicants argue mainly that the instant specification is enabled for the method as claimed because Applicants have clearly demonstrated that the anti-proliferative effects of type I IFN are increased in transfected human HT 1080 cells *in vitro* as well as in an *in vivo* model using transfected LOX human melanoma cells. Applicants further argue that a recent publication by the inventors also clearly indicate that transfection of human MDA231 cells with the IFNAR2c gene increases he sensitivity of these cells to treatment with a type I IFN. Applicants also argue that the specification also teaches that the IFNAR2c gene may be delivered to the organism in any effective manner, and that different methods that are useful for the introduction of an exogenous gene into human cells such as electroporation with naked DNA or plasmid DNA or delivery of viral vectors into cells both *in vitro* and *in vivo* are well known to those of skill in the art as evidenced by the teachings of Qin et al that describes the use of viral vectors to deliver IFNβ to tumors *in vivo* with resultant tumor regression.

Firstly, it is noted that although the introduction of a gene into a cell *in vitro* was routine and conventional at the effective filing date of the present application, targeting a gene into any human target cell population *in vivo* by any route of delivery (an embodiment of the instant rejected claims) to attain desired therapeutic effects was neither routine nor predictable as evidenced by the teachings of Dang et al., Verma & Somia, Romano et al. and Xu et al.

Secondly, it is noted that in both *in vivo* models using the transfected LOX human melanoma cells and the transfected human MDA231 cells, these tumor cell lines were transfected *in vitro* and **NOT *in vivo***, and thus they do not provide any guidance for a skilled artisan in the art on how to overcome hurdles involved *in vivo* vector targeting known in the art to achieve desired therapeutic effects. Similarly, the article of Qin et al teaches specifically **direct *in vivo* IFN-β gene delivery into established tumors** (see abstract), and not by any route of delivery that includes a systemic delivery of the IFN-β gene.

Accordingly, claims 28-41 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 30, it is unclear what is encompassed by the terms "type I c –IFN", type I R-IFN" and "type I w-IFN". These terms are not commonly found in the art? Clarification is requested because the metes and bounds of the claim are not clearly determined.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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QUANG NGUYEN, PH.D
PATENT EXAMINER